without prejudice, and have amended Claims 4, 11, 27 and 41. Support for amended Claims 4, 11, 27 and 41 can be found generally throughout the instant Specification and in Claims 1-57 as filed. Attached hereto is a marked-up version of the changes made to Claims 4, 11, 27 and 41 by the instant Amendment. The attached page is captioned "**Version With Markings To Show Changes Made**."

The Invention is Enabled

Claims 1-52 and 59-65 have been rejected 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the instant Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the instant Invention. The Examiner has asserted that for one of skill in the art to practice the full scope of the claimed invention, the public would have to finely tune the reaction conditions to where a plurality of primers can be used and wherein at least one of the primers will have a mismatch with the target sequence on the 3' terminus. The Examiner also believes that simultaneously, the mismatch primer must not also effectively anneal to non-target sequences so as to result in the amplification of non-target sequences. The Examiner also contends that such fine tuning of target reaction conditions are imperative to practice the claimed invention. The Examiner has also asserted that the pending Claims have sufficient breadth of scope so as to encompass virtually any reaction condition, and that the situation in hand is apposite to that set forth in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001 (Fed Cir. 1997).

In response, Applicants respectfully submit that the instant Application readily provides sufficient information to enable one of ordinary skill in the art to practice Applicants' Invention, and that the underlining facts of *Genentech, Supra.* are entirely ***inapposite*** to the instant situation.

For example, in *Genentech, Supra.,* the court stated:

> The question before us is whether the specification would have enabled a person having ordinary skill in the art at the time of filing to use cleavable fusion expression to make hGH without undue experimentation. There is no dispute that the portion of the specification chiefly relied upon by Genentech and by the district court, column 7, lines 29-59, does not describe in any detail ***whatsoever*** how to make hGH using cleavable fusion expression....The relevant portion of the specification merely describes three (or perhaps four) applications for which cleavable fusion expression is *generally* well-suited and then names an enzyme that might be used as a cleavage agent (trypsin), along with sites at which it cleaves....Thus, the specification does not describe a specific material to be cleaved or any reaction conditions under which cleavable fusion expression would work.

Genentech, Supra., at page 1004 (emphasis added).

In stark contrast, the instant Specification readily provides specific information regarding reaction steps. Indeed, as previously explained to the Examiner, the instant Specification provides specific information regarding solvents (page 62, lines 11-17); pH ranges and buffers (page 62, lines 18-21, page 63, lines 1-13); temperatures (page 63, lines 14-21 and page 64, lines 1-3); the number of PCR cycles; the time for the reaction; and the concentration of various reagents, materials used, e.g., primers, polynucleotides, nucleosides, etc. (page 64 through to page 67) for practicing the instant Invention. Furthermore, unlike *Genentech, Supra.*, disclosed in the instant Specification is ***a specific example***. Hence, the instant Specification discloses sufficient information to enable one of ordinary skill to practice Applicants' Invention without the performance of undue experimentation. One of ordinary skill in the art may need to perform, ***at most, routine*** experimentation to practice the instant Invention, if at all. "...[O]mission of minor details does not cause a specification to fail to meet the enablement requirement."

Genentech, Supra. at page 1005.

In addition, the Examiner has reiterated his position of the previous office action, i.e., that undue experimentation is required to practice the instant Invention. In maintaining this position, the Examiner has again relied upon the test for undue experimentation set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). However, the Examiner has again ***not*** made a *prima facie* case that undue experimentation is required to practice the instant Invention. For example, the Examiner has again asserted that the nature of the instant Invention relates to matters of physiology and chemistry, which the Examiner believes are unpredictable and require "greater levels of enablement." In support of this position, the Examiner has cited *In re Fisher*, 166 USQP 18 (CCPA, 1970). However, it is respectfully submitted that the quotation the Examiner reproduced from *Fisher, Supra.,* to support the Examiner's assertion was taken out of context, and was recited by the court in *Fisher, Supra.* in response to an issue that is not relevant to the instant Application. In particular, it is explained on page 23 of *Fisher, Supra.* that the phrase "at least 1 international unite of ACTH per milligram" recited in a claim before that court was an "open ended" recitation because it had a lower limit, but no upper limit. The court noted that the specification provided an upper limit of 230% of standard. Hence, it was the court's opinion that the inventor should be allowed to dominate the future patentable inventions of others where those inventions were based in some way on the inventor's teachings. However, the court also held that the inventor did not enable the preparation of ACTHs having potencies much greater than 2.3. *Fisher, Supra.* at 23-24. It was in support of this holding regarding the open-ended recitation that the court stated the quotation the Examiner relied upon in making this rejection. However, there is no such so-called open ended Claim pending in the instant Application. The

Examiner cited *Fisher, Supra.* merely to support his ***conclusion*** that the nature of the instant Invention is inherently unpredictable. However, the Examiner has not provided any ***evidence*** to support this conclusion. Thus, the Examiner has not made a *prima facie* case that the nature of the instant Invention is inherently unpredictable.

Furthermore, the Examiner has asserted that in Applicants' previously filed response, Applicants had cast references cited in the instant Specification as disclosing essential subject matter. It is the Examiner's opinion that enablement cannot be achieved by incorporating by reference non-US patent documents that have not issued as a patent. The Examiner also asserted that even in the case where US patent applications have been identified, currently pending as well as abandoned applications cannot be relied upon for disclosing essential subject matter.

In response, it is respectfully submitted the Examiner is incorrect in asserting that Applicants have "cast" the references cited on pages 7-10 of the instant Application as containing "essential" subject matter. Rather, these references were pointed out to the Examiner in order to refute the Examiner's position that at the time the instant Application was filed, the state of the art was not developed sufficiently to permit a skilled artisan to practice the instant Invention without performing undue experimentation. In particular, the Examiner is directed to page 5 of the July 19, 2001 response, wherein Applicants explain:

> Pages 7-10 of the instant Application describe numerous pieces of prior art that were available at the time of filing, that are relevant to the instant Invention. Particular examples include, but certainly are not limited to WO 94/04706 (Kievits *et al.*), who teach adding a control sequence to a PCR reaction; Gilliland *et al.* (PNAS **87**:27525-2729 (1990)), who disclose the use of competitive polymerase chain reaction; Teleenti *et al.* (J. Virol. Methods **39**:259-268 (1992), who describe a competitive polymerase chain reaction using an internal standard; and U.S. Patent 5,043,272,

which describes the amplification of nucleic acid sequences using oligonucleotides of random sequence as primers.

Consequently, in light of Applicants' previously made arguments reproduced in part above, the Examiner is clearly not correct in asserting that Applicants' previous argument "cast" these references as containing "essential" subject matter for practicing the instant Invention.

Furthermore, the Examiner has maintained his position that a Ph.D. is required to practice the instant Invention and has not found Applicants' previous arguments convincing, i.e., that the level of skill in the art to as high as PCR is taught in undergraduate courses. In particular, the Examiner believes that Applicants' remarks in this regard are conclusory in nature and are void of any factual underpinning. Moreover, the Examiner has asserted that no college catalog has been provided which identified PCR as being taught in any undergraduate class. It is the Examiner's position that Kary B. Mullis, Ph.D., Nobel laureate, is the inventor of PCR, and is considered to be representative of the level of skill in the art needed to practice the instant Invention. Hence, the Examiner believes the level of skill required to practice the instant Invention is high and that pursuant to *Genentech*, *Supra.* undue experimentation is required to practice the instant Invention.

In response, Applicants respectfully submit that the Examiner has provided no evidence to support his position that a Ph.D. is required to practice the instant Invention. Thus, it is the Examiner's statements, and not Applicants', that are conclusory. The Examiner has the burden of showing that the degree of knowledge needed to practice the instant Invention is high, on par with that of a Ph.D. He has made no such showing. Instead, he has asked Applicants to support their statement that PCR is taught in undergraduate classes. In essence, the Examiner has

required Applicants to ***disprove*** the Examiner's unsupported and conclusory statements. Despite being under no obligation to disprove the Examiner's conclusory statement, Applicants submit herewith a copy of the syllabus for an undergraduate biochemistry laboratory course being taught this spring at the University of South Florida in Tampa, FL. This syllabus makes clear that PCR is indeed taught at the ***undergraduate*** level (see laboratory of April 8th). Hence, the Examiner is clearly ***not correct*** in asserting a Ph.D. is required to practice the instant Invention.

In addition, the Examiner has once again asserted that the absence of starting materials and reaction conditions which would enable the full scope of the instant Invention unfairly shifts the burden of enablement from that of applicant to the public. Hence, it is the Examiner's position again that the one example set forth in the instant Specification is not sufficient in enabling the pending Claims, and that the instant matter is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001.

However, as explained above, unlike the situation described in *Genentech, Supra.*, Applicants have clearly provided reaction conditions and starting materials, e.g., primers, polynucleotides, nucleosides, etc. for practicing the instant Invention. Moreover, as Applicants have previously explained to the Examiner, MPEP §2164.02 states that the example need only be "prophetic." Furthermore, it has been judicially held that the specification need not even contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without performing undue experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). However, as explained above, unlike in *Genentech, Supra.*, Applicants ***have*** provided an example of their Invention. Thus, *Genentech, Supra.* is clearly inapposite to the instant matter, and as explained above and throughout the instant

response, undue experimentation is not required to practice the instant Invention.

Furthermore, Claims 53-57 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the instant Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the instant Application as filed, had possession of the claimed Invention. The Examiner has asserted that as presently worded, the kit of Claims 53-57 has sufficient breadth of scope to encompass primers that will hybridize to any and all possible target sequences, be they known or unknown. It is the Examiner's opinion that the instant Specification does not reasonably suggest that Applicants were in possession of any and all primer combinations as presently claimed. Thus, it is the position of the Examiner that the instant Specification does not satisfy the written description requirement set forth in 35 U.S.C. § 112, first paragraph. In this amendment, Applicants have canceled Claims 53-57, without prejudice. Thus, this rejection is MOOT.

Moreover, Claims 4-6, 11-13, 27-29, 41-43 and 53-57 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly the subject matter which Applicant regards as the Invention. The Examiner has asserted the term "substantially" recited in claims 4, 11, 27, 41 and 53 is a relative term that renders the claims indefinite. In particular, the Examiner believes that (1) the term "substantially" is not defined by the pending Claims, (2) that the instant Specification does not provide a standard for ascertaining the requisite degree, and (3) that one of ordinary skill in the art would not be reasonably apprised of the scope of the instant Invention. Furthermore, the Examiner has asserted that Claims 5-6, 12-13, 42-43 and 54-57 are also indefinite for being dependent upon Claims 4, 11, 27, 41 and 53.

Moreover, The Examiner has explained that he has considered Applicants' arguments

previously made in response to this rejection, i.e. that the pending Claims define the term "substantially," but does not consider them to be convincing. In particular, although the Examiner has acknowledged that the pending Claims indicate some modification at the 3' terminus, it is the Examiner's position that the phrase "substantially identical" is separate and apart from the characterization at the 3'-terminus of the modified oligonucleotide primer. Thus, it is the Examiner's opinion that this term is indefinite.

Applicants respectfully traverse this rejection. As explained above, Claims 53-57 have been canceled, without prejudice. Thus, the rejection of these Claims is MOOT. Moreover, Applicants have amended Claims 4, 11, 27 and 41 so that they no longer recite the term "substantially." Hence, this rejection should be withdrawn.

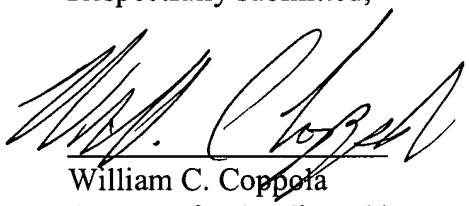
Fees

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

CONCLUSION

Applicant respectfully requests entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,



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Version With Markings To Show Changes Made

Material that is underlined is to be added, and material within brackets is to be removed.

4. (Amended) The method of Claim 2 wherein a modified oligonucleotide primer is included in said combination where said modified oligonucleotide primer is [substantially] identical to said oligonucleotide primer except for [but contains] a chemical modification at its 3'-end that prevents degradation, by said 3' to 5' exonuclease, of said 1 to 10 nucleotides.

11. (Amended) The method of Claim 9 wherein a modified oligonucleotide primer is included in said combination wherein said modified oligonucleotide primer is [substantially] identical to said first or said second primer except for a chemical modification at its 3'-end that prevents degradation by said 3' to 5' exonuclease, of said 1 to 10 nucleotides.

27. (Amended) The method of Claim 25 wherein a modified oligonucleotide primer is included in said combination wherein said modified oligonucleotide primer is [substantially] identical to said one of said primers except for a chemical modification at its 3'-end that prevents degradation, by said 3'-5' exonuclease, of said 1 to 10 nucleotides.

41. (Amended) The method of Claim 39 wherein a modified oligonucleotide primer is [substantially] identical to said oligonucleotide primer except for a chemical modification at its 3'-end that prevents degradation, by said 3'-5' exonuclease, of said 1 to 10 nucleotides.